REMARKS

Claims 1-33 and 68-70 are pending in the application. Claims 5-7 and 10-11 have been withdrawn. Claims 1-4, 8, 9, 12-33, and 68-70 have been examined. Claim 33 is allowed. Claims 1-4, 8, 9, 12-32, and 68-70 stand rejected. Claims 1-3, 5-12, 18, 20, 22, 24-27, 30-32, and 68-70 have been amended. Reconsideration and allowance of Claims 1-4, 8, 9, 12-32, and 68-70 is respectfully requested.

The Rejection of Claims 1-4, 8, 9, 12-32 and 68-70 Under 35 U.S.C. § 112, Second Paragraph (Indefiniteness)

Claims 1-4, 8, 9, 12-32, and 68-70 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

To clarify the claimed invention, Claim 1, from which Claims 2-4, 8, 9, and 12-32 depend, has been amended as follows:

> 1. A method for determining the magnitude of a measurable response elicited by an agent in living cells, the method comprising the steps of:
>
> (a) obtaining an expression measurement of at least one gene population or at least one protein population in living cells contacted with an agent and generating at least one of an efficacy value of the agent, a toxicity value of the agent or a classifier value of the agent;
>
> (b) making at least one comparison selected from the group consisting of:
>
> (1) comparing the efficacy value of the agent to at least one reference efficacy value to yield an efficacy comparison result, wherein each efficacy value represents at least one expression pattern of the same efficacy-related population of genes, or at least one expression pattern of the same efficacy-related population of proteins;
>
> (2) comparing the toxicity value of the agent to at least one reference toxicity value to yield a toxicity comparison result, wherein each toxicity value represents at least one expression pattern of the same toxicity-related population of genes, or at least one expression pattern of the same toxicity-related population of proteins; and

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(3) comparing the classifier value of the agent to at least one reference classifier value to yield a classifier comparison result, wherein each classifier value represents at least one expression pattern of the same classifier population of genes, or at least one expression pattern of the same classifier population of proteins;

(c) using the comparison result(s) obtained in step (b) to determine the magnitude of the response elicited by the agent in living cells ; and

(d) presenting the magnitude of the response obtained in step (c) to a user.

Support for the phrase "the magnitude of a measurable response elicited by an agent in living cells" is found throughout the specification as filed, for example at page 7, line 23, to page 8, line 9, and page 47, lines 12-16.

Support for the phrase in step (c) "to determine the magnitude of the response elicited by the agent in living cells" is found throughout the specification as filed, for example, at page 25, line 16, to page 26, line 3; page 46, line 31, to page 48, line 21; page 63, line 30, to page 64, Table 3; page 115, line 3 to page 117, line 3; and Table 13.

Support for the phrase in step (d) "presenting the magnitude of the response obtained in step (c) to a user" is found throughout the specification as filed, for example at page 46, line 31, to page 48, line 21; and page 57, lines 19-31; and page 65, line 3, to page 102, line 5.

Dependent Claims 2, 3, 5-12, 18, 20, 22, 24, 25, 26, 27, 30-32 have been amended to incorporate the claim language of Claim 1, as amended.

Claims 68 and 69 have been amended to replace the phrase "defined biological response" with the phrase "measurable biological response."

Claim 70 has been amended to replace the term "known" with the term "reference." Support for this amendment is found in the specification at page 41, line 10-29.

Removal of this ground of rejection is respectfully requested.

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The Rejection of Claims 1-4, 8, 9, and 12-32 Under 35 U.S.C. § 101

Claims 1-4, 8, 9, and 12-32 stand rejected under 35 U.S.C. § 101. The Examiner contends that the rejected claims do not produce any tangible result because the method may take place entirely within the confines of a computer or human mind without communication to the outside world and without using or making available for use the results of the computation. While not acquiescing to the Examiner's position, but in order to facilitate prosecution, Claim 1, from which Claims 2-4, 8, 9, and 12-32 depend, has been amended to include step (d) which recites "presenting the magnitude of the response obtained in step (c) to a user," thus obviating the rejection. Ample support for this amendment is found in the specification as filed, for example, at page 46, line 31, to page 48, line 21; and page 57, lines 19-31; and page 65, line 3, to page 102, line 5. Removal of this ground of rejection is respectfully requested.

The Rejection of Claims 1-4, 12-16, 18-26, 28 and 30-32 Under 35 U.S.C. § 102(b) as Being Anticipated by International Publication No. WO 02/059560 A2 (Castle et al.)

Claims 1-4, 12-16, 18-26, 28, and 30-32 stand rejected under 35 U.S.C. § 102(b) as being anticipated by International Publication No. WO 02/059560 A2 (Castle et al.). Applicants traverse this rejection for the following reasons.

While not acquiescing with the Examiner's position, but in order to facilitate prosecution, Claim 1, from which Claims 2-4, 12-16, 18-26, and 30-32 depend, has been amended as mentioned above, to recite at step (c) "using the comparison result(s) obtained in step (b) to determine the magnitude of the response elicited by the agent in living cells," and new step (d) "presenting the magnitude of the response obtained in step (c) to a user."

It is respectfully submitted that Castle et al. does not anticipate the claimed invention as amended. In order to anticipate, the reference must disclose, either expressly or inherently, each and every element of the claim. M.P.E.P. § 2131.

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Castle et al. is directed to the use of a toxicological algorithm using a logistic regression (binary) method to provide a predictive model regarding the toxicity of a substance. As described in Castle et al., the logistic regression analysis only deals with *a binary categorical outcome* (*e.g.*, only 0 to 1, toxic or not). For example, at page 9, lines 10-16, Castle et al. states:

> [t]he summary scores are subjected to logistic regression analysis, resulting in a predictive model. In this aspect of the embodiment, the input data are the summary scores per sample, which is an indicator for each sample; the analysis is a logistic regression analysis mapping the summary scores to a 0 to 1 scale of toxicity, and the out put data are one or more mathematical formulae that converts a column of average differences into *a single 0 to 1 toxicological score* for a sample.
>
> (Emphasis added.)

In sharp contrast to the teachings of Castle et al., the claimed invention is directed to comparing at least one of an efficacy value of an agent, a toxicity value of an agent, or a classifier value of an agent to at least one of a reference efficacy value, a reference toxicity value or a reference classifier value, respectively, and using the comparison result(s) to determine the *magnitude of the response* elicited by the agent in living cells. Therefore, in contrast to the teachings of Castle et al, which are directed to logistic regression resulting in a binary categorical outcome, the methods of the invention are used to obtain a *continuous outcome* (*e.g.*, through the use of chi-square fitting approach to generate interval/ratio data), which allows for the computation of a magnitude of biological activity in order to identify and rank agents that possess a desired therapeutic profile with regard to efficacy and/or toxicity. For example, the methods of the claimed invention may be used to identify glucose lowering agents that have activity ranging from full agonist to partial agonist, weak agonist activity, or no agonist activity. See, *e.g.*, Example 1, page 57, line 19, to page 64, line 3; and Table 3.

Appended hereto as Exhibit A is a Declaration of Dr. Yejun Tan ("the Tan Declaration") which describes an experiment that was carried out using the methods described in the

application as filed (see specification, e.g., at page 57, line 18, to page 117, line 3) demonstrating that the claimed invention was used to rank a panel of 79 candidate compounds with respect to magnitude of response (gamma activation index), in comparison to a known PPAR gamma agonist, as shown in Exhibit A, Figure 1. In contrast to the claimed method, the binary method described in Castle would not allow one to identify partial agonists or rank compounds in terms of magnitude of response.

Therefore, it is respectfully submitted that the teachings of Castle et al., fail to anticipate or suggest the methods of the claimed invention, as amended. Removal of this ground of rejection is respectfully requested.

The Rejection of Claims 8, 9, 17, 27, 29, and 68-70 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Castle et al. in View of Mukherjee et al. (*Molecular Endocrinology* 14:1425-1433 (2000))

Claims 8, 9, 17, 27, 29, and 68-70 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Castle et al. in view of Mukherjee et al. (*Molecular Endocrinology* 14:1425-1433 (2000)). The Examiner contends that the combination of Castle et al. and Mukherjee et al. taken as a whole, teach all of the required elements of the instantly rejected claims. The Examiner acknowledges that Castle et al. does not teach partial agonist activity with respect to a biological response, nor does it teach partial agonist activity with respect to PPAR-gamma, use of 3T3L1 adipocyte cells, or production of an efficacy related gene pattern. The Examiner cites Mukherjee et al. as disclosing a that a correlation exists between PPAR-gamma affinity and the "minimum effective dose" required to lower glucose levels in diabetic rodent models. The Examiner asserts that it would have been obvious to one of ordinary skill to modify the toxicological algorithm of Castle et al. to determine and classify the activity of an agent by use of the PPAR-gamma analysis of Mukherjee et al. because, while both studies examine rodent cells,

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Mukherjee et al. has the advantage of exemplifying a correlation of the relations between the required agents, cell species, and the efficacy in treating diabetes related complications.

Applicants disagree with the Examiner's conclusion for at least the following reasons.

It is submitted that the Examiner has failed to establish a *prima facie* case of obviousness because even if the references were to be improperly combined, the combined references do not teach or suggest all the elements of the claimed invention. As noted above, Claim 1, from which Claims 8, 9, 17, 27, and 29 depend, has been amended to clarify that the claimed invention is directed to methods for determining the *magnitude of a measurable response* elicited by an agent in living cells (*e.g.*, through the use of chi-square fitting approach to generate interval/ratio data), which allows for the computation of a magnitude of biological response in order to identify agents that possess a desired therapeutic profile with regard to efficacy and/or toxicity. In contrast, as noted above, the teachings of Castle et al, are directed to logistic regression resulting in only a binary categorical outcome, without providing information regarding the magnitude of response. With regard to Claim 68, from which Claims 69-70 depend, as acknowledged by the Examiner, Castle et al. does not teach partial toxicity values in order to analyze agent toxicologies.

The teachings of Mukherjee et al. fail to cure the deficiencies of Castle et al. noted above.

The Examiner has cited the Mukherjee et al. reference as disclosing that a correlation exists between PPAR-gamma affinity and the "minimum effective dose" required to lower glucose levels in diabetic rodent models. It is noted that even if one were to improperly combine the teachings of Castle and Mukherjee et al., as proposed by the Examiner, which there is no motivation to do, the method of Castle modified with the teachings of Mukherjee would not result in the claimed invention for at least the following reasons.

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As described in the Tan Declaration, Exhibit A, the Mukherjee et al. reference discloses a correlation approach (i.e., the linear association of one variable compared with another variable), and does not teach or suggest the comparison methods of the present invention (such as a chi-square fitting approach which measures how large in magnitude one variable differs compared to another variable, i.e., the slope between the best fitting line and the x-axis), which provides a magnitude of response of an agent. The difference between a correlation approach and the comparison approach of the present invention is illustrated in Exhibit A, FIGURE 2, which demonstrates that a chi-square fitting method of comparison allows a ranking to be established between two partial agonists (P1 and P2) based on the magnitude of response, whereas the correlation approach taught by Mukherjee et al. would not provide this information. Therefore, even if the references were to be improperly combined, the combination does not teach or suggest a method for determining the *magnitude of a measurable response* elicited by an agent in living cells, and therefore does not disclose or suggest all the limitations of the claimed method.

Moreover, there is no motivation to combine the referenced teachings because there is no expectation of success. With regard to the Castle reference, applicants disagree with the Examiner's assertion that Castle et al. discloses the determination of an efficacy value by assigning the agent a classification such as that shown in FIGURE 1 of Castle et al. In contrast to the Examiner's assertion in this regard, it is noted that the teachings of Castle et al. are directed to *toxicity profiling*. For example, as stated in Castle et al., "[t]he present invention, a method and system for expression similarity profiling for *predictive toxicology*, employs a number of different methods for multivariate statistical analysis." Page 28, lines 12-14 (emphasis added).

Further, as applicants previously pointed out in the response to non-final office action filed on May 17, 2007, the passages of Castle et al. that refer to FIGURE 1 merely refer to

"patterns" that are "relevant to the toxicological process" (see Castle et al. at page 7, lines 12-13; page 8, lines 10-17; and page 9, lines 3-7). As stated in Castle et al. at page 10, lines 3-5, "[I]n correlating these other studies, one preferably compare gene lists for *patterns of interest* between studies of related compounds to arrive at *a consensus set of genes involved in a toxicological response*" (emphasis added).

The Examiner also asserts that the term "response" on page 7, lines 12-13, of Castle et al., "indicates an overexpression, underexpression or plateau effect of the chemical on a gene. While one of the responses for each gene is construed as a toxic response, the opposite response is construed as effective." Page 18 of the Non-Final Office Action mailed August 7, 2007. Applicants respectfully disagree with the Examiner's interpretation of the term "response" and wish to point out that in the context of the teachings of Castle et al. when taken as a whole, the opposite of a toxic response is believed to be a non-toxic response, and not an efficacy response, as construed by the Examiner.

With regard to the Mukherjee et al. reference, it is submitted that the teachings of Mukherjee et al. would lead one away from the claimed method of the invention because there is no reasonable expectation of success provided for the use of *transcriptional expression profiling* to determine whether an agent possesses biological activity with respect to PPARγ.

Mukherjee et al. describes the characterization of a novel PPARγ ligand (LG100641) that was *identified in a protein binding assay* (see page 1431) and does not teach or suggest the use of transcriptional expression profiling to determine whether an agent elicits a measurable response in living cells, as claimed. In fact, it is submitted that the teachings of Mukherjee et al. would actually lead one of skill in the art away from the claimed method of the invention. As described in Mukherjee et al., the novel compound LG100641 was initially identified as a PPARγ ligand in *a protein binding assay*. As further described in Mukherjee et al., it discloses the "identification

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of a compound, LG100641 that binds to PPARγ *but does not activate gene expression.*" Page 1425 (emphasis added). As further described in Mukherjee et al., "LG100641-bound PPARγ is *transcriptionally silent*." Page 1429 (emphasis added).

Accordingly, there is no motivation to combine the referenced teachings, and even if the teachings of Castle et al. and Mukherjee et al. were to be combined, which there is no suggestion or motivation to do, the combination does not teach or suggest all the elements of the invention as claimed.

Therefore, in view of the above, it is demonstrated that the combination of Castle et al. and Mukherjee et al. does not render obvious Claims 8, 9, 17, 27, 29, and 68-70. Accordingly, the Examiner is respectfully requested to withdraw this combination of references as a ground for rejection under 35 U.S.C. § 103(a).

Allowable Subject Matter

Applicants thank the Examiner for the indication that Claim 33 is allowed.

CONCLUSION

In view of the foregoing remarks, applicants submit that all of the pending claims are in condition for allowance and notification to this effect is respectfully requested.

Respectfully submitted,

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